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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/606,222	THOMAS ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 November 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *20-24,32 and 43-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *20-24, 32, 43-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment, filed 11/10/2003 has been entered.

Claims 20-24, 32, 43-57 are pending and under current examination.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 43-57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for deleting a marker sequence from a DNA sequence that has been introduced into an mouse *ES* cell genome, whereby the sequence is deleted utilizing a *gamete-specific* promoter, said DNA molecule comprising a recombinase site, a gamete-specific promoter operably linked to a recombinase gene, a *marker* DNA, and a recombinase site, the method comprising growing the ES cell to develop into a mouse, such that that when the gamete-specific promoter is active during gametogenesis, the recombinase gene is expressed in the mouse and the marker gene is deleted in the resulting gametes, and transgenic mice comprising a nucleic acid sequence comprising in sequential order: a recombinase site, a gamete-specific promoter operably linked to a recombinase gene, a *marker* DNA, and a recombinase site, wherein the DNA molecule has been stably integrated into the genome of the transgenic mouse. The specification does

not reasonably provide enablement for the breadth of the claims encompassing methods for deleting nucleic acid sequences from a DNA molecule that has been introduced into a mouse cell genome, whereby said sequence is deleted in a regulatable manner utilizing a regulatable promoter, said DNA molecule comprising in sequential order: a recombinase site, a regulatable promoter operably linked to a recombinase gene, a foreign DNA, a recombinase site, the method comprising growing said cell such that the regulatable promoter is active, said recombinase gene is expressed in the cell and said foreign DNA is deleted and transgenic mice comprising the DNA molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The specification teaches that the claimed vector is to be used for the self-excision of nucleic acid sequences in a tissue specific manner. For example, utilizing a gamete-specific promoter, such as a testes-specific promoter, or an ovary-specific promoter, such that the excision of the nucleic acid sequence(s) occur during gametogenesis. In another example, the foreign DNA may be excised in specific somatic tissue growth of the organism. The foreign DNA can be heterologous DNA, such as a marker sequence, or a wild-type allele for use in gene therapy, wherein its presence in the germline or specific tissues of a transgenic organism is not desired. See p. 4, lines 13-19. The specification teaches that the instant method can be used

for the generation of knockout animals, because marker genes may unpredictable affect the phenotype, the removal of marker genes is desired. See p. 7, lines 17-19. The specification teaches that the instant method could also be used to generate mice harboring conditional-mutant alleles, in agricultural crops, and in *in utero* human gene therapy to correct genetic deficiencies. See p. 8.

The claimed invention is not enabling for the following reasons: the working example of the specification teach the generation of knockout mice by expression of the described construct with a testes-specific promoter from the angiotensin-converting enzyme gene to drive the expression of the Cre-recombinase gene to delete the neomycin marker gene. The breadth of the claims encompasses the deletion of any nucleic acid sequence from any mouse cell; however, the specification fails to provide teachings or guidance to enable this breadth. The specification contemplates utilizing the described method in somatic cells to excise foreign DNA in specific somatic tissues during the growth of the organism, and that the foreign DNA may be either a marker or a wild-type allele. This is not enabling, because the specification fails to teach or provide guidance as to how a wild-type allele would be used in the claimed method utilizing somatic cells. Only ES cells would be capable of being used in the claimed method, because somatic cells would be unable to undergo the extensive rounds of selection required by the instant method. Secondly, because the methods result in the deletion of the construct sequence upon expression of the tissue specific marker, it is unclear how a wild-type allele would

be expressed, since it would be deleted upon the expression of Cre. For example, the specification teaches that the DNA molecule can, "comprise a gene which is desired to be incorporated and expressed in an organism." See p. 4, lines 29-30. Further, is unclear how the foreign DNA in the construct could be anything other than a marker gene. The cells that express the foreign DNA must be selected for [see Figure 1, for example]; without this step of selection, it would be unclear how cells that have integrated the construct would be selected for.

The claims recite that the promoter is a *regulatable* promoter. This is not enabling because all promoters are regulatable; that is, they are regulated by factors in the cell, or factors provided exogenously. The enabled scope of the promoter, with regard to the claimed invention is found to be a gamete-specific promoter. This is because the claimed invention is found to be enabling for the generation of knockout mice by selection of mice whose gametes express the described construct.

Accordingly, in view of the specification's lack of teaching or guidance with regard to the deletion of a nucleic acid sequence from any mouse cell, other than a mouse ES cell, the lack of teaching or guidance with regard to utilizing any regulatable promoter, other than a gamete-specific promoter, and utilizing any foreign DNA, other than a marker sequence, to produce transgenic mice, it would have required unduce experimentation for one of skill in the art to make and use the claimed invention.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 43-48 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 43, as written, is unclear. The claim recites "a foreign DNA". It is unclear what the term "foreign" means. Foreign to the construct, or to the recipient animal it would be used in, or foreign to both? It would appear that "foreign" is dependent upon the context in which the molecule would be used. Furthermore, the term foreign DNA encompasses any sequence, expressed or not, even a few base pairs. Claims 44-48 depend from claim 43.

Claim Rejections - 35 USC § 102

The prior rejection of claims 1-6, 20-24, 32, 38-41, 43-45 are rejected under 35 U.S.C. 102(e) as being anticipated by US Pat. No. 6,537,805 B1 [Melchner *et al.*] is *withdrawn* in view of Applicants' arguments and/or amendment to the claims. A new rejection under 35 USC 102 appears below.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 20-24, 32 and 43-45 are rejected under 35 U.S.C. 102(b) as being anticipated by Russ *et al.* [**J. Virol.**, 70(8):4927-4932 (1996)].

The claims are directed to a nucleic acid molecule for removing a foreign DNA that has been inserted into a host cell, the molecule comprising in sequential order (a) a recombinase site, (b) a regulatable promoter operably linked to (c) a recombinase gene (d) the foreign DNA and (e) a recombinase site. In further embodiments, the recombinase site can be loxP or FRT and the recombinase gene can be Cre or FLP.

Russ teach the generation of a retroviral vector having duplication of terminal control regions U5 and U3 to generate LTRs, utilizing Cre positioned between two loxP target sequences to exise most of the viral and nonviral sequences unrelated to the transcription of the U3 gene. See *Abstract.* Russ teach the southern blot analysis of NIH 3T3 cells expressing the U3pgklxtkneoMCCre proviruses. See Figure 3. Russ further teach that the vectors pggSVCreU3lxpgkpuro and pggSVCreU3lxSVpuro were used to transfect BOSC23 cells to obtain an infectious virus, and the titers of the recovered viruses were determined on NIH3T3 cells by selection of puromycin. They teach that genomic

DNA of the puromycin-resistant colonies were analyzed and it was found that in 12 of 14 recombined clones, the sequences flanked by *loxP* were absent, indicating the recombination of the proviruses. See figure 4, and particularly 4B. Russ further discuss that the self-deleting retroviral constructs can have additional selectable markers to allow for the selection of both provirus integration and recombination. See p. 4930, 1st column, 3rd ¶, last sentence.

Accordingly, Russ anticipate the claimed invention.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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